

WHAT IS CLAIMED IS:

1. A method of synergistically enhancing the chemotherapeutic treatment of cancer expressing adenosine A₃ receptors comprising administering to a mammal in need thereof an effective amount of a high affinity adenosine A₃ receptor antagonists either prior to or during administration of a chemotherapeutic cancer agent.

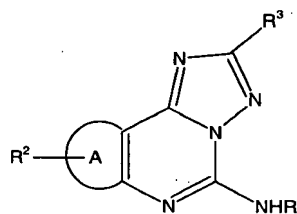
2. The method of claim 1 wherein the chemotherapeutic cancer agent is a taxane family compound.

3. The method of claim 1 wherein the chemotherapeutic cancer agent is a vinca alkaloid compound.

4. The method of claim 1 wherein the chemotherapeutic cancer agent is a camptothecin compound.

5. The method of claim 1 wherein the chemotherapeutic cancer agent is an antibiotic compound.

6. The method of claim 1 wherein the high affinity adenosine A₃ receptor antagonist is a compound of formula:



wherein:

A is imidazole, pyrazole, or triazole;

R is -C(X)R¹, -C(X)-N(R¹)₂, -C(X)OR¹, -C(X)SR¹, -SO_nR¹, -SO_nS R¹, or -SO_n-N(R¹)₂;

R¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, heterocyclic, lower alkenyl, lower alkanoyl, or, if linked to a nitrogen atom, then taken together with the nitrogen atom, forms an azetidine ring or a 5-6 membered heterocyclic ring

containing one or more heteroatoms;

R² is hydrogen, alkyl, substituted alkyl, alkenyl, aralkyl, substituted aralkyl, heteroaryl, substituted heteroaryl or aryl;

R³ is furan, pyrrole, thiophene, benzofuran, benzypyrrole,

5 benzothiophene, optionally substituted with one or more

substituents selected from the group consisting of hydroxy,

acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl,

substituted alkoxy, substituted alkenyl, substituted alkynyl,

amino, substituted amino, aminoacyl, acyloxy, acylamino,

10 alkaryl, aryl, substituted aryl, aryloxy, azido, carboxyl,

carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy,

heterocyclic, heterocycloxy, aminoacyloxy, thioalkoxy,

substituted thioalkoxy, -SO-alkyl, -SO-substituted alkyl, -SO-

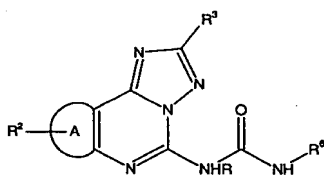
aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-

15 aryl, -SO₂-heteroaryl, and trihalomethyl;

X is O, S, or NR¹; and

pharmaceutically acceptable salts thereof.

7. The method of claim 1 wherein the high affinity adenosine A₃ receptor
20 antagonist is a compound of formula:



wherein:

A is imidazole, pyrazole, or triazole;

25 R² is hydrogen, alkyl, substituted alkyl, alkenyl, aralkyl, substituted aralkyl, heteroaryl, substituted heteroaryl or aryl; R³ is furan; and

R⁶ is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle or substituted heterocycle; and

pharmaceutically acceptable salts thereof.

- 30 8. The method of claim 6 wherein R² is selected from the group consisting of

hydrogen, alkyl, alkenyl and aryl.

9. The method of claim 6 wherein A is a triazolo ring.

5 10. The method of claim 6 wherein A is a pyrazolo ring.

11. The method of claim 1 wherein the cancer is selected from the group consisting of human leukemia, melanoma, pancreatic carcinoma, breast carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, lung carcinoma, histiocytic lymphoma, astrocytoma and keratinocytoma.

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12. A method of synergistically enhancing the chemotherapeutic treatment of cancer expressing adenosine A₃ receptors comprising administering to a mammal in need thereof an effective amount of a high affinity adenosine A₃ receptor antagonists either prior to or during administration of a chemotherapeutic cancer agent wherein the cancer has multi-drug resistance that is P-glycoprotein dependent.

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13. The method of claim 11 wherein the chemotherapeutic cancer agent is a taxane family compound.

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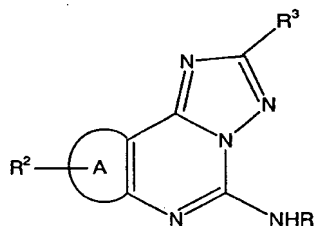
14. The method of claim 11 wherein the chemotherapeutic cancer agent is a vinca alkaloid compound.

25 15. The method of claim 11 wherein the chemotherapeutic cancer agent is a camptothecin compound.

16. The method of claim 11 wherein the chemotherapeutic cancer agent is an antibiotic compound.

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17. The method of claim 11 wherein the high affinity adenosine A₃ receptor antagonist is a compound of formula:



wherein:

A is imidazole, pyrazole, or triazole;

R is -C(X)R¹, -C(X)-N(R¹)₂, -C(X)OR¹, -C(X)SR¹, -SO_nR¹, -SO_nS R¹, or -
 5 SO_n-N(R¹)₂;

R¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl,
 alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl,
 heterocyclic, lower alkenyl, lower alkanoyl, or, if linked to a
 10 nitrogen atom, then taken together with the nitrogen atom,
 forms an azetidine ring or a 5-6 membered heterocyclic ring
 containing one or more heteroatoms;

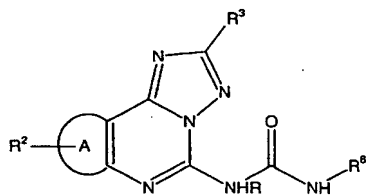
R² is hydrogen, alkyl, substituted alkyl, alkenyl, aralkyl, substituted
 aralkyl, heteroaryl, substituted heteroaryl or aryl;

R³ is furan, pyrrole, thiophene, benzofuran, benzopyrrole,
 15 benzothiophene, optionally substituted with one or more
 substituents selected from the group consisting of hydroxy,
 acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl,
 substituted alkoxy, substituted alkenyl, substituted alkynyl,
 amino, substituted amino, aminoacyl, acyloxy, acylamino,
 20 alkaryl, aryl, substituted aryl, aryloxy, azido, carboxyl,
 carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy,
 heterocyclic, heterocycloxy, aminoacyloxy, thioalkoxy,
 substituted thioalkoxy, -SO-alkyl, -SO-substituted alkyl, -SO-
 aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-
 25 aryl, -SO₂-heteroaryl, and trihalomethyl;

X is O, S, or NR¹; and

pharmaceutically acceptable salts thereof.

18. The method of claim 11 wherein the high affinity adenosine A₃ receptor
 30 antagonist is a compound of formula:



wherein:

A is imidazole, pyrazole, or triazole;

R² is hydrogen, alkyl, substituted alkyl, alkenyl, aralkyl, substituted aralkyl, heteroaryl, substituted heteroaryl or aryl; R³ is furan;

5 and

R⁶ is heteroaryl or substituted heteroaryl; and
pharmaceutically acceptable salts thereof.

19. The method of claim 16 wherein R² is selected from the group consisting of
10 hydrogen, alkyl, alkenyl and aryl.

20. The method of claim 16 wherein A is a triazolo ring.

21. The method of claim 16 wherein A is a pyrazolo ring.

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22. The method of claim 11 wherein the cancer is selected from the group consisting of human leukemia, melanoma, pancreatic carcinoma, breast carcinoma, prostate carcinoma, colon carcinoma, ovarian carcinoma, lung carcinoma, histiocytic lymphoma, astrocytoma and keratinocytoma.

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23. A method of synergistically enhancing the chemotherapeutic treatment of cancer expressing adenosine A₃ receptors comprising administering to a mammal in need thereof an effective amount of a high affinity adenosine A₃ receptor antagonist and a adenosine-5'-triphosphate depleting agent either prior to or
25 during administration of a chemotherapeutic cancer agent wherein the cancer has multi-drug resistance that is P-glycoprotein dependent.

24. The method of claim 21 wherein the adenosine-5'-triphosphate depleting agent consists of a compound selected from the group consisting of L-alanosine
30 and adenosine kinase inhibitors.

25. The method of claim 21 wherein the adenosine-5'-triphosphate depleting agent consists of a compound or a salt of a compound selected from the group consisting of 2-deoxyglucose, cyanine, oligomycin, valinomycin, and azide.
- 5 26. A method of treating skin carcinoma comprising administering to a human patient in need thereof an effective amount of a high affinity adenosine A₃ receptor antagonist either prior to or during administration of a chemotherapeutic cancer agent wherein the chemotherapeutic cancer agent is a taxane family compound.
- 10 27. The method of claim 24 wherein the high affinity adenosine A₃ receptor antagonist is administered in a topical application.